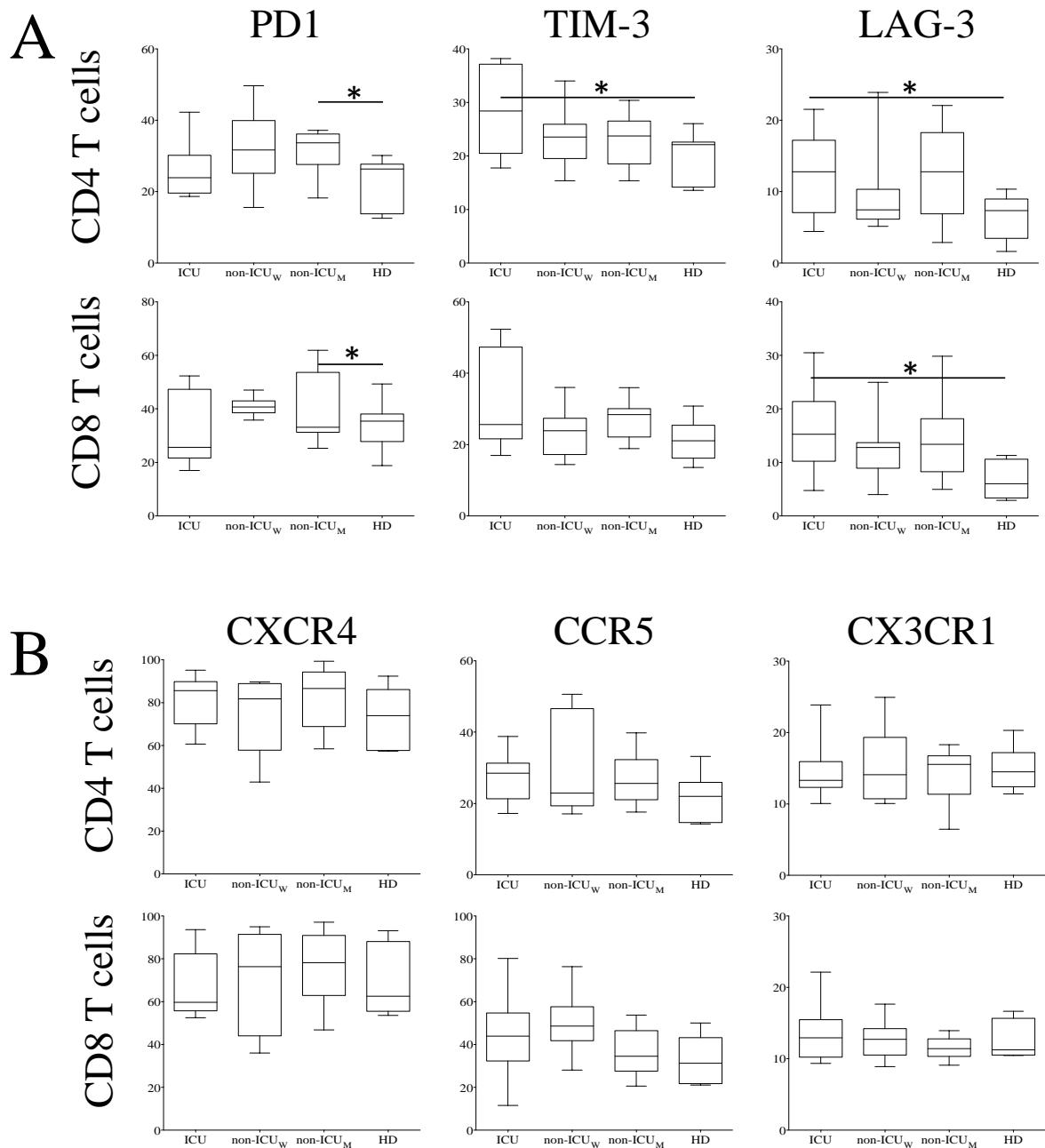
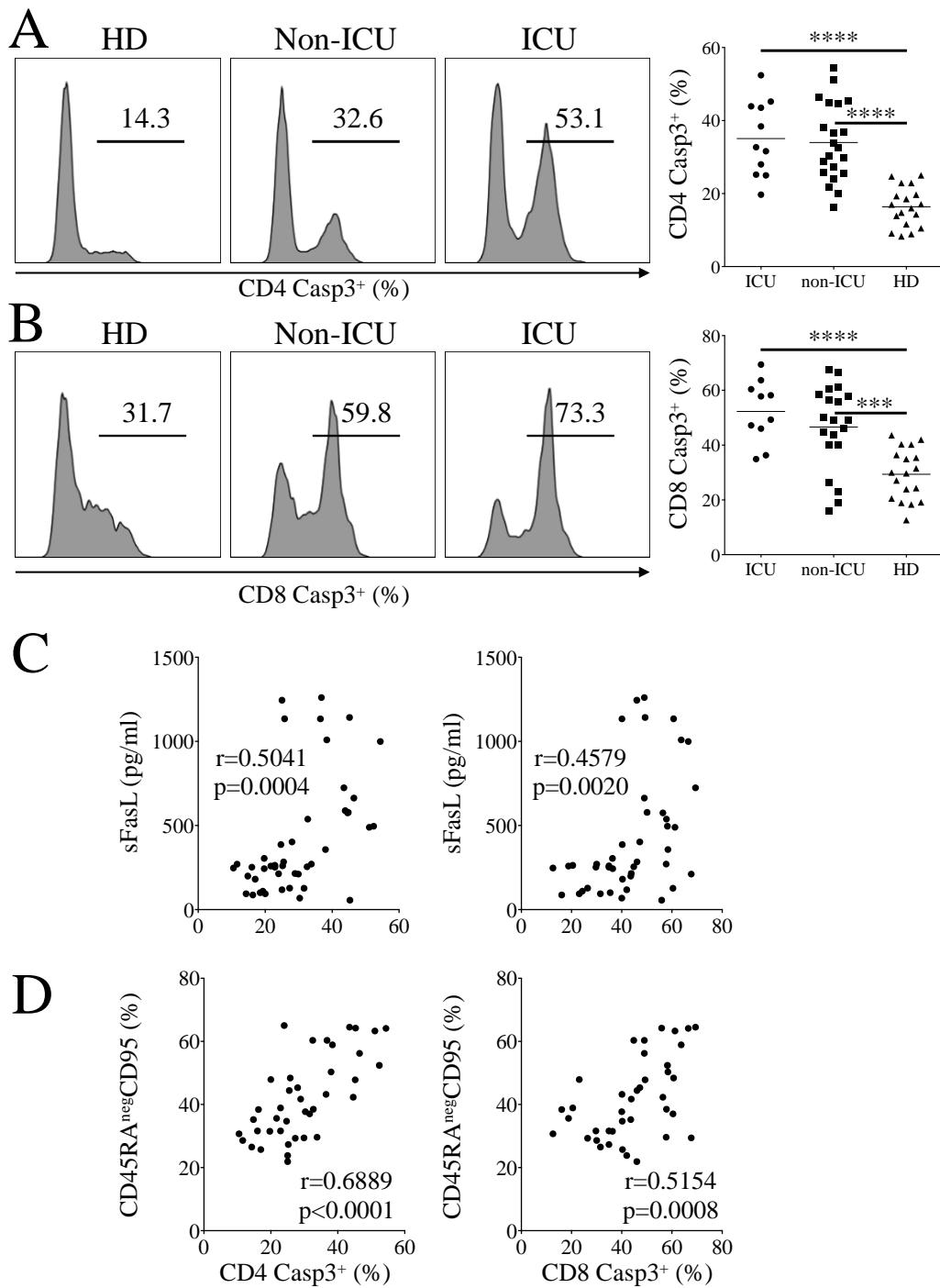


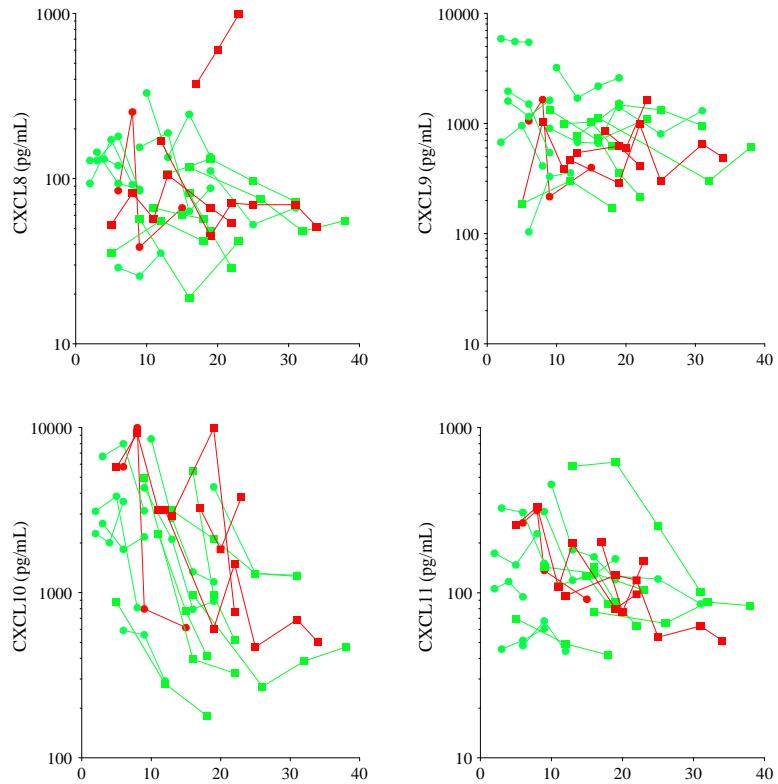
**Supplementary Figure 1: CD95 expression on B cells.** A) Gating strategy. B cells are defined by CD20+HLA-DR+ expression gating from CD3negCD8neg cells. B) Dot-plots showed CD95 expression on CD21+ B cells in HD, non-ICU and ICU individuals.



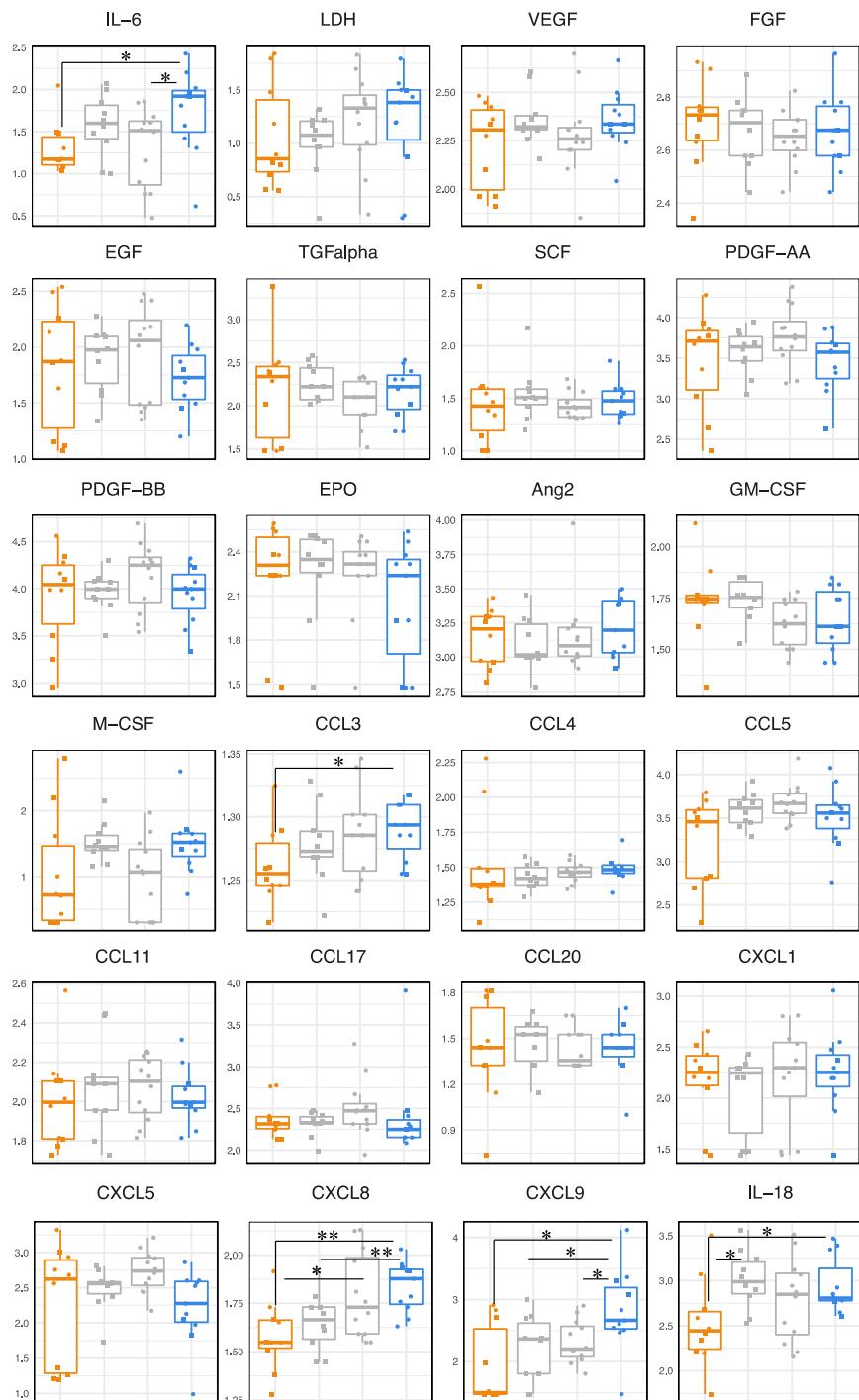
**Supplementary Figure 2.** Expression of exhaustion markers and chemokine receptors. A) Percentages of CD4 and CD8 T cells expressing exhaustion markers, PD1, TIM-3 and LAG-3, in ICU, non-ICU<sub>W</sub> (women) and non-ICU<sub>M</sub> (men) patients and HDs. B) Percentages of CD4 and CD8 T cells expressing chemokine receptors, CXCR4, CCR5 and CX3CR1. Statistical analysis was performed using a Mann-Whitney U test. \*p<0.05.



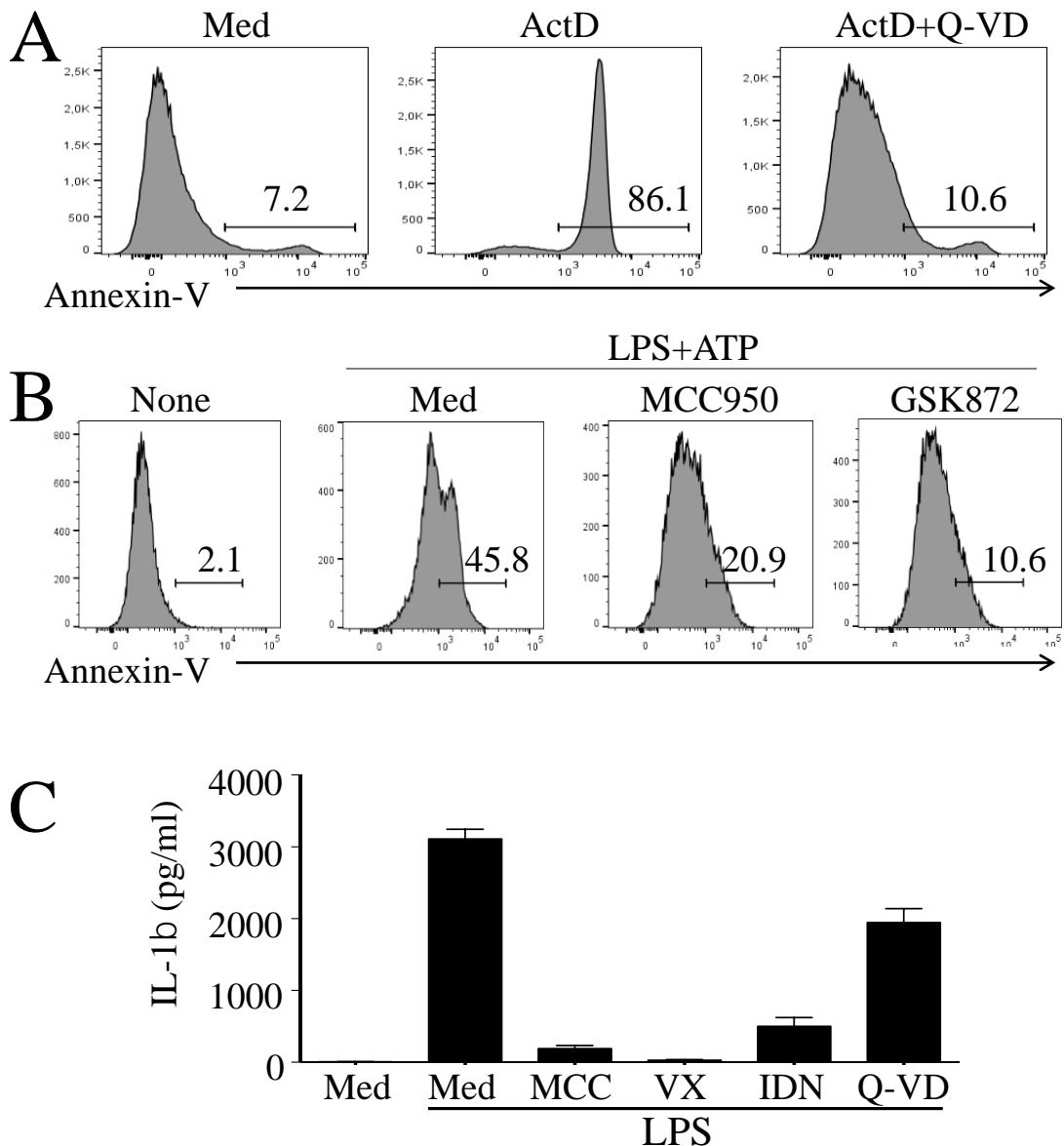
**Supplementary Figure 3: Caspase-3 activation in T cells correlates with plasma sFasL and CD95 in COVID 19 patients.** (A and B) Caspase activity of CD4 and CD8 T cells was quantified by flow cytometry using fluorescent caspase-3 substrate. Percentages of CD4 (A) and CD8 T cells (B) expressing fluorescent caspase substrates are shown. Each dot represents one individual. Statistical analysis was performed using a Mann-Whitney U test. \*\*\* $p<0.001$  and \*\*\*\* $p<0.0001$ . C) Correlation between plasma sFasL and caspase-3 activation in CD4 and CD8 T cells. D) Correlation between the percentages of CD45RA<sup>-</sup> T cells expressing CD95 and caspase-3 activation in CD4 and CD8 T cells. Values of Spearman correlation are shown in the panels.



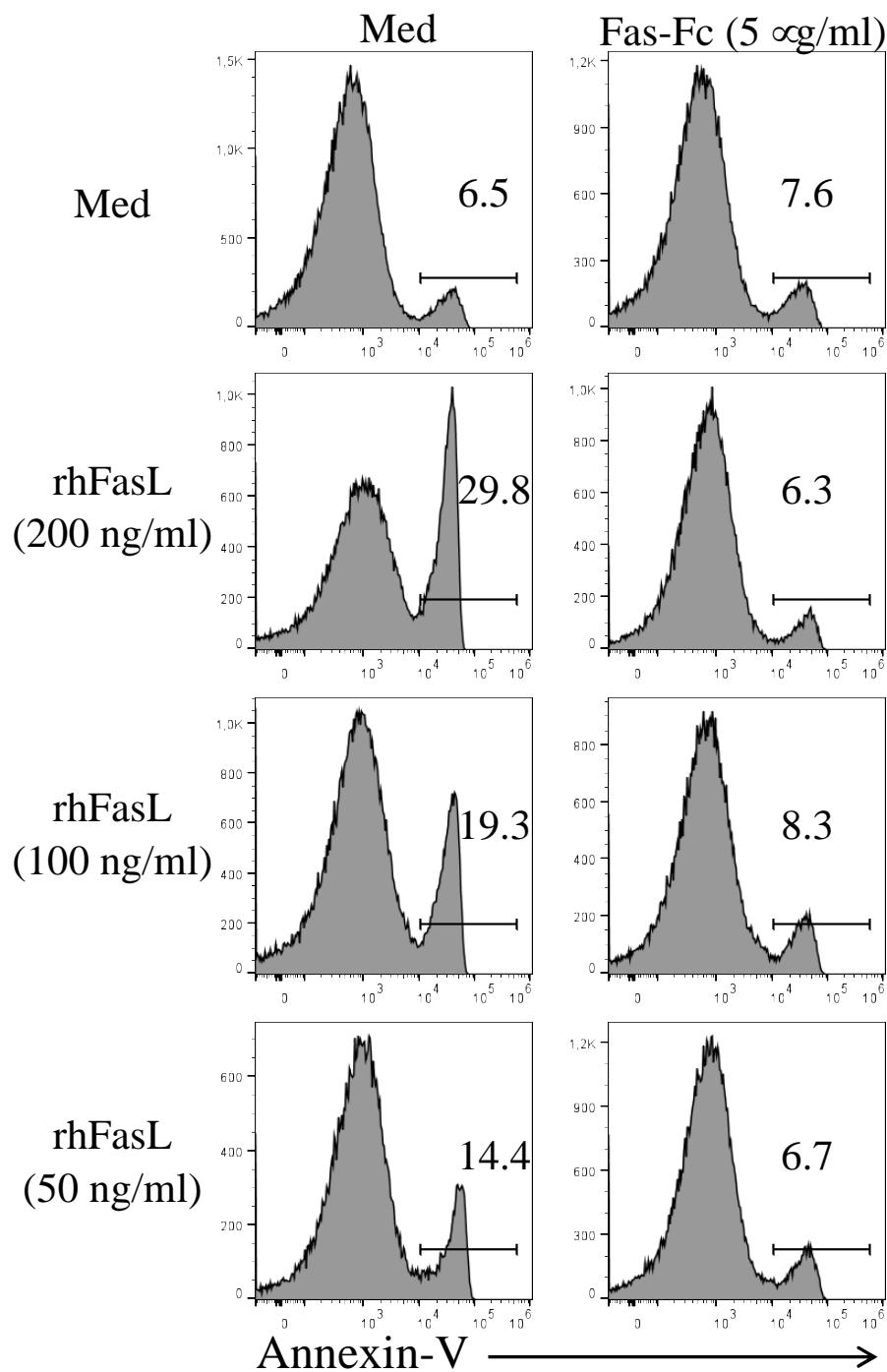
**Supplementary Figure 4. Dynamics of cytokines in the sera of COVID-19.** Cytokines were quantified in patients with severe infection (ICU, red) and with middle severity (non-ICU). Samplings were performed at different timepoints post symptomatology. Nine women and nine men were followed along the course of the disease.



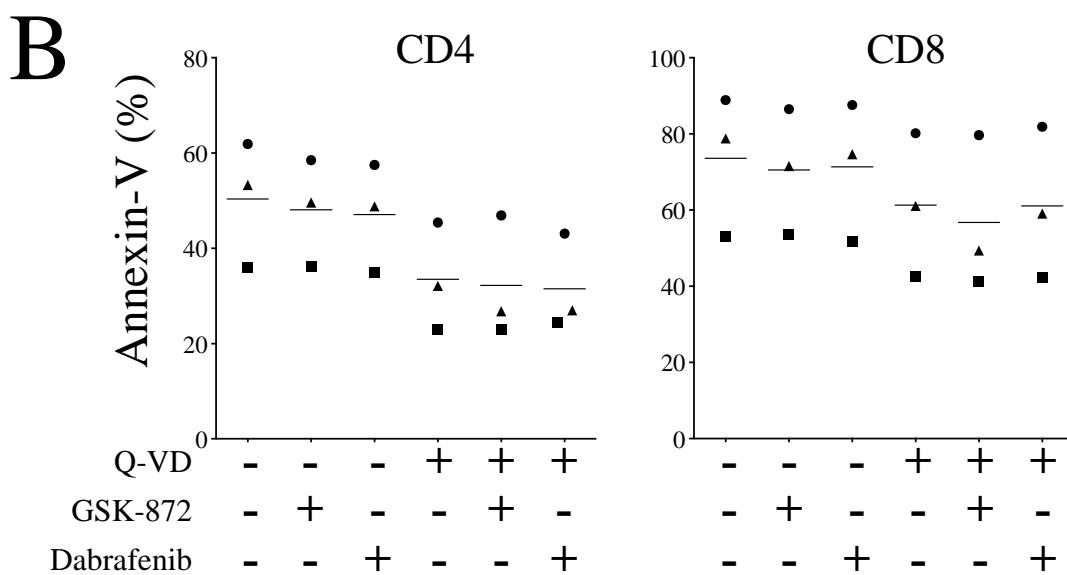
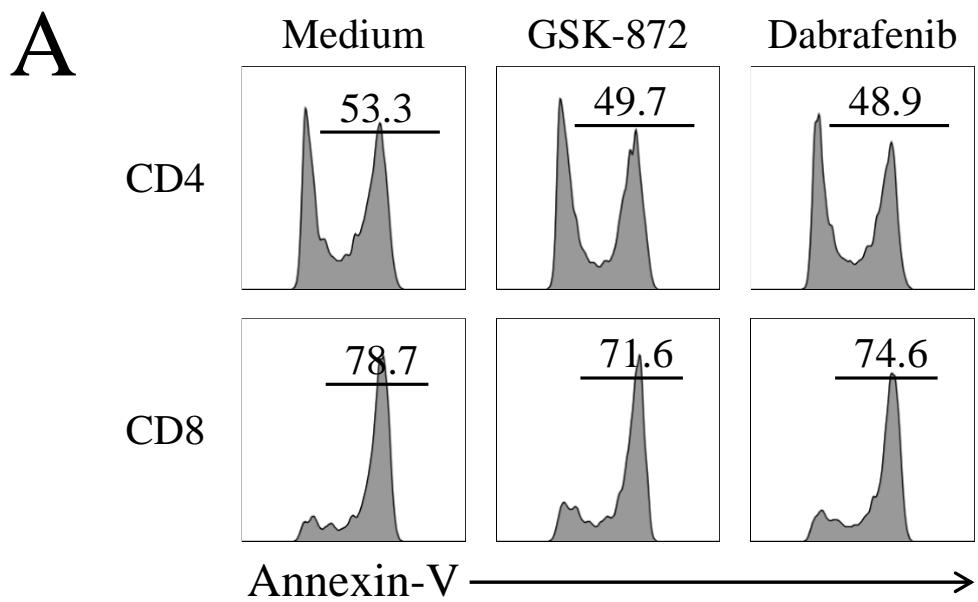
**Supplementary Figure 5. Boxplots of the LFQ intensity values of cytokines for each patient.** y-axis represents cytokine concentrations (pg/mL). Color represents the patient groups (orange: HD; gray: non-ICU; blue: ICU) and marker shapes represent sex (squared: men Boxplot2; rounded: women Boxplot3). Significant variations between groups based on a Student's t-test are showed above each graph (\*\* p<0.05; \*\*\* p<0.01).



**Supplementary Figure 6.** A) THP-1 cells are treated for 8 hrs with actinomycin D (ActD, 2.5  $\mu$ M) in the absence or presence of Q-VD (10  $\mu$ M). Cell death was scored with annexin V-FITC staining by flow cytometry. Results are representative of at least two independent experiments. B) For necroptosis, THP-1 cells are primed with LPS (1  $\mu$ g/ml) for 6 hr and then treated 2 hrs with ATP (40  $\mu$ M). Cells were incubated in the absence or presence of either MCC950 (2  $\mu$ M) or GSK872 (2  $\mu$ M). Samples were scored with annexin V-FITC by flow cytometry. Data are representative of at least three independent experiments performed. C) PBMC are either unstimulated (Med) or stimulated overnight with LPS (1  $\mu$ g/ml) in the absence or presence of MCC950 (1  $\mu$ M), VX-765 (10  $\mu$ M), IDN-6556 (10  $\mu$ M), and Q-VD (10  $\mu$ M). Supernatants are collected and IL-1 $\beta$  quantified by ELISA. Histogram is the mean of four healthy donors.



**Supplementary Figure 7.** Jurkat cells are treated for 8 hrs with different doses of recombinant human FasL (rhFasL) in the absence or presence of Fas-Fc (5  $\mu$ g/ml). Cell death is scored with annexin V-FITC staining by flow cytometry. Results are representative of at least two independent experiments.



**Supplementary Figure 8: RIPK3 inhibitors and T cell death.** (A) Flow cytometry of CD4 and CD8 T cells from COVID-19 patients. (B) Percentages of CD4 and CD8 T cells expressing annexin-V are shown. Each symbol represents one individual. Cells were cultured in the absence or presence of Q-VD (10  $\mu$ M) and incubated with or without GSK-872 (2  $\mu$ M) and Dabrafenib (2  $\mu$ M).

Antibody	Clone	Brand
CD3-vioblu	REA 613	Miltenyi Biotec
CD3-V500	SP34-2	BD Biosciences
CD3-PE-Cy7	SP34-2	BD Biosciences
CD8-PE	RPA-T8	BD Biosciences
CD8-PE-Cy7	RPA-T8	BD Biosciences
CD8-AF700	SK1	Biolegend
CD20-PE	2H7	BD Biosciences
CD20-PE-Cy7	2H7	BD Biosciences
CD20-APC-Vio770	REA 780	Miltenyi Biotec
CD20-APCH7	2H7	BD Biosciences
CD95-APC	DX2	Miltenyi Biotec
HLA-DR-PerCP-Vio700	REA 805	Miltenyi Biotec
CD45RA-PE-Vio770	REA 562	Miltenyi Biotec
CD4-ef450	OKT4	eBiosciences

Supplementary Table 1: Antibodies used.

Cytokine	Kit, Brand
IL-18	Human Total IL-18, R&D System
FasL	Human Fas Ligand/TNFSF6, R&D System
sCD14	Human sCD14, R&D System
CXCL13	Human CXCL13/BLC/BCA-1, R&D System
IL-1Ra	Human IL-1ra/IL-1F3, R&D System
TRAIL	Human TRAIL/TNFSF10, R&D System
IL-6	Human IL-6, R&D System
CXCL8, CXCL10, CCL11, CCL17, CCL2, CCL5, CCL3, CXCL9, CXCL5, CCL20, CXCL1, CXCL11, CCL4	Human Proinflammatory chemokine panel, Biolegend
Angiopoietin-2, EGF, EPO, FGF, G-CSF, GM- CSF, HGF, M-CSF, PDGF-AA, PDGF-BB, SCF, TGF- $\alpha$ , VEGF	Human growth factor panel, Biolegend

Supplementary Table 2: Cytokines, chemokines and factors tested in this study

TNF- $\alpha$	FP : AGGCAGTCAGATCATCTTCTC RP : GTTGCTACAAACATGGGCTAC
IFN- $\gamma$	FP : TTGGAAAGAGGAGAGTGACAG RP : CATGTCTCCTGATGGTCTC
BAK	FP : CGCTGGGGAGACTGATAACT RP : TGGCCTCAGGTAGAATGGTG
BAX	FP : GAGCTGCAGAGGGATGATTGC RP : TGGCAAAGTAGAAAAGGGCG
BCL-2	FP : ACTGGTGGAGGATGGAAAGG RP : CCCAGGGCAGATTTCCAAA
RIPK1	FP : TGGCGTCATCATAGAGGAAG RP : CGCCTTTCCATGTAAGTAGCA
RIPK3	FP : AATTCTGCTGCGCCTAGAAC RP : TCGTGCAGGTAAAACATCCC
MLKL	FP : AGGAGGCTAATGGGGAGATAGA RP : TGGCTTGCTGTTAGAAACCTG
RPS18	FP : CTGCCATTAAGGGTGTGG RP : TCAATGTCTGCTTCCTCAAC
GAPDH	FP : CAACTACATGGTTACATGTTCC RP : GAAGATGGTGATGGGATTTC

Supplementary Table 3: primers used to quantify mRNA transcripts